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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/935,061	08/21/2001	Brian K. Kobilka	STAN-213	7757

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EXAMINER	
LI, RUIXIANG	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,061	KOBILKA ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20-24* is/are allowed.

6)☒ Claim(s) *1-3 and 5-13* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicants' amendment filed on 04/14/2005 has been entered in full. Claims 2 and 8 have been amended. Claims 1-23 and 20-24 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 2-4 and 8 under 35 U.S.C. 112, second paragraph, as set forth at page 2 of the previous Office Action (Paper No. 01212005, mailed on 01/25/2005), has been withdrawn in view of amended claims.

The objection to claim 8 has been withdrawn in view of amended claim.

Claims Rejections under 35 U.S.C. 102(b)

Claims 1-3 and 9-12 are rejected under 35 U.S.C. 102 (b) as being anticipated by Dunham et al. (J. Biol. Chem. 274:1683-1690, 1999).

Dunham et al. teach conformational changes in rhodopsin upon photoactivation using a series of of rhodopsin mutants containing single reactive cysteine residues in the cytoplasmic side of helix F (3rd intracellular loop)(see Fig. 1; abstract; the middle of right column of page 1685), including the mutant V250C; such a conformational change exposes the cytoplasmic loops and allows transducin to bind and become activated (2nd paragraph of right column of page 1683). The cysteine mutants were studied in two ways, by measuring their reactivity to a cysteine-specific reagent (PyMPO-maleimide) and by labeling the cysteins with a fluorescence label (monobromobimane) followed by fluorescence spectroscopic analysis (Abstract). Since the fluorescence change was measured in a 4-mm black jacketed cuvette containing 0.08% DβM (a detergent; left column of page 1685), the rhodopsin receptor would be in a membrane of detergent micelles (see page 13 of the instant specification for definition) and attached to cuvette (a immobilization phase), via either the N-terminal portion or C-terminal portion. Dunham et al. also teach that the rhodopsin antagonist, 11-cis-retinal, is covalently bound in the middle of helices, inactivating the protein in the dark state. Light causes the isomerization of 11-cis retinal to the all-trans form and activates the receptor (page 1683). Dunham et al. further teach that the conformational change described in the study is a conserved ad primary step in the activation of GPCRs, such as β-adrenergic receptor (right column of page 1689), and that the approaches used in the study should be applied to measurement of conformational changes of other GPCRs (top of page 1690). Thus, the reference of Dunham et al. meets the limitations of claims 1-3 and 9-12.

Claims Rejections under 35 U.S.C. 103(a)

(i). Th following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 5-8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunham et al. (J. Biol. Chem. 274:1683-1690, 1999) as applied to claims 1-3 and 9-12 above, and further in view of Farrens et al. (Science 274:768-770, 1996).

Dunham et al. teach detection of conformational changes in rhodopsin upon photoactivation using a series of of rhodopsin mutants containing single reactive cysteine residues in the cytoplasmic side of helix F as applied to claims 1-3 and 9-12 above. The rhodopsin mutants taught by Dunham et al. were expressed in COS-1 cells (right column of page 1685).

Dunham et al. do not teach a protease cleavage site within rhodopsin as a conformationally sensitive detectable probe and the protease cleavage products.

Farrens et al. teach detecting photoactivated conformational changes in rhodopsin using spin-labeled double cystein mutants. Each contains one cysteine at the cytoplasmic end of helix C (Cys^{139}) and one cysteine at various positions in the cytoplasmic end of helix F (see Abstract; Fig. 1). Farrens et al. also teach that rhodopsin

has two sites of V-8 proteolysis; one site is located within the conformationally sensitive third intracellular domain (see, e.g., Fig. 1). After V-8 digestion, rhodopsin was cleaved primarily into two large fragments: an N-terminal fragment (~27 kD) and a C-terminal fragment (~13 kD) on SDS-PAGE (Figs. 1 and 3). Since there are two sites of V-8 proteolysis, the fragment of ~13 kD, which was detected by SDS-PAGE analysis, can be considered to be an epitope tag.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Dunham et al. to use the V-8 proteolysis, instead of a fluorescence label, as a conformationally sensitive probe to detect conformational change of rhodopsin with a reasonable expectation of success. One would have been motivated to do so because the site of V-8 proteolysis is located in the third intracellular domain and is confirmationally sensitive as taught by Farrens et al. and the fragments of V-8 proteolysis can be readily analyzed by SDS-PAGE as demonstrated by Farrens et al.

Claim Objection

Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 20-24 are allowable.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
June 23, 2005